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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,242	04/01/2004	James Freddo	PC25581A	9207

28940 7590 06/13/2008

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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
06/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,242	FREDDO ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,12-16,32,36,37,39-41 and 49-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,12-16,32,36,37,39-41 and 49-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/17/08 has been entered.

The response filed **3/17/08** presents remarks and arguments to the office action mailed **10/18/07.** Applicants' request for reconsideration of the rejection of claims in the last office action has been considered.

Applicants' arguments, filed, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of Claims

Claims 8, 12-16 and 32, 36-37, 39-41 and 49-53 are pending in this office action.

Claims 52-53 are newly added.

Claim Rejections - 35 USC § 102 are withdrawn as the ranges are narrower than the ranges recited in the prior art.

New Claim Rejections - 35 USC § 103

Applicant relies on the unexpected result to overcome the claim rejection. Based on re-evaluation of the documents in support of unexpected result, the exhibits relied upon did not show unexpected result because Applicant's argument is that the concentrations used are different from the prior art. This is found not persuasive see for example:

6.1.5. Single Agent Anti-tumor Efficacy in Human Renal Carcinoma

SN12C-GFP renal carcinoma model: AG-013736 was investigated for its anti-tumor activity in GFP transfected human renal carcinoma tumors that were orthotopically transplanted and grown in the kidneys of mice. Two days after tumor transplantation, AG-013736 was administered at 10, 30, and 100 mg/kg dose levels via the PO, BID regimen for either 42 days or 72 days. The green fluorescent signal of the tumor was measured intermittently throughout the treatment period and whole body optical images of GFP-expressing metastases were acquired at the end of the study. Table 2 summarizes the results of the study. Treatment with AG-013736 at 30 and 100 mg/kg, but not 10 mg/kg, clearly resulted in statistically-significantly smaller primary tumor mass than the vehicle control on both termination days ($p < 0.05$). TGIs from the 10, 30, and 100 mg/kg dose groups were 54%, 56%, and 63% for the 41-day treatment arm, respectively, TGIs from these dose groups were 61%, 74%, and

6.1.4. Single Agent Anti-tumor Efficacy in Human Melanoma Models

Anti-tumor efficacy against established A375 melanoma tumor: The A375 human melanoma model was used to further evaluate the activity of AG-013736 against large and established tumors (Study DDH-MG-268). A375 tumors were established via sc implantation and the treatment was initiated when average tumor size reached about 350 mm^3. AG-013736 treatment at 10 and 30 mg/kg resulted in dose-dependent growth delay of 38% and 59%, respectively, compared to the vehicle-treated control tumors (Figure 4A). Although somewhat less than what was typically observed from studies where dosing was initiated when tumors were smaller, anti-tumor efficacy of AG-013736 at 30 mg/kg dose level against the established A357 tumors was statistically significant compared to the control group ($p = 0.035$).

Studies in the M24met melanoma model: M24met human melanoma model is an aggressive human melanoma that spontaneously metastasizes to lymph nodes and lungs in mice. The model was used frequently in the laboratory because it offered the possibility of evaluating multiple efficacy end points including primary tumor growth, metastasis, and survival of animals. Removing the primary tumors promoted the metastasis potential. Also important is that the M24met cells express mutant p53 and are reported to express high levels of oncogenic molecules such as N-RAS, ERK, as well as a3b1-integrins that are involved in tumor migration, adhesion and survival,[36] the cells do not express functional VEGFR but a low level of phospho-PDGFRs (Table 1).

First investigated was whether AG-013736 could inhibit the growth of primary M24met tumors implanted subcutaneously in nude mice (Study DDH-163). At dose levels of 3, 10, and 30 mg/kg, AG-013736 (PO, BID) significantly delayed tumor growth (Table 1) with TGIs of 60%, 69%, and 73%, respectively. Statistically, TGIs for the 3 and 10 mg/kg AG-013736 groups were not different from each other ($P = 0.4$), whereas the TGI in the group receiving 30 mg/kg AG-013736 was significantly greater than that of the 10 mg/kg dose group ($p = 0.033$).

The second investigation determined whether AG-013736 could inhibit metastasis when M24met was intradermally implanted in SCID (Balb/c) mice. The M24met cells (2.5×10^6) were implanted intradermally in the lower right flank of SCID mice. When the primary tumors reached the size of 300 – 400 mm^3 (usually ~ 2 weeks after implantation), they were surgically removed to promote distant metastasis. For the "Early Treatment" arms, the dosing of AG-013736 (30 mg/kg, PO BID) started one week prior to the primary tumor removal. For the "Late Treatment" arms, the treatment started 1 day before the primary tumor removal. The total treatment time was 3 weeks for all groups. At the end of the study, the metastatic tumors in the lymph nodes (mainly in the ipsilateral and counter-ipsilateral sites, with occasional tumors found in the inguinal sites) were weighed and stained for CD-31 by IHC. Lungs were

and other examples in exibit 2 shows the drug is administered as 3,10 and 30 mg/kg. See above On page 67

2.1.3. *Axitinib (AG-013736)*

Axitinib is an oral inhibitor of the receptor tyrosine kinases VEGFR1, VEGFR2, PDGFR and c-KIT (Table 1) given at a dose of 5 mg twice daily [60]. A phase 2 study of axitinib in metastatic renal cell carcinoma has been reported in abstract form (ASCO 2006 Abstract 4509, Rini *et al.*). Fifty-two patients entered the study; eligibility criteria included failure of one prior cytokine-based therapy. A partial response to treatment was reported in 24 patients (46%). With a median follow up of 1 year, only 1 patient with a PR had relapsed [after 232 days of therapy]. Reported grades 1 or 2 toxicities were nausea (29%), fatigue (29%), diarrhoea (27%), weakness (19%), anorexia (17%) and weight loss (15%). Hypertension was reported in 17 patients (33%); 12% of patients had grades 3 or 4 hypertension and 6% of patients had aggravated hypertension.

shows the administration of 5 mg but was not compared to other dosage ranges, so unexpected result is not shown, infarct the

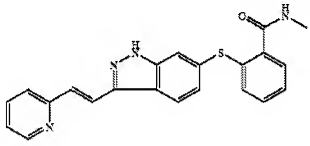
exhibits show ranges within the Kania claimed ranges to be effective in treating renal cancer, example 30 mg/Kg.

The rejection is therefore maintained and repeated.

This rejection is repeated as the rejection was prematurely withdrawn by the Examiner.

Claims 8, 12-13 15-16, 32, 36-37, 39-41 and 49-53 are rejected under 35 U.S.C. 103(a) in the last Office Action as being unpatentable over Kania et al. WO 2001/02369, now a US Patent 6,531,491 (all of record) in view of Sweeney et al. Cancer Res. 61 3369-3372, 2001 further in view of Goodman and Gilman.

Kania et al. teach methods of treating cancer and other disease states associated with unwanted angiogenesis and/or cellular proliferation (see abstract), administering a compound of formula 1 as shown below to a mammal (see col. 16, lines



25+)

(see col. 11 lines 35+)in a

pharmaceutically acceptable salt, solvate (see col. 13, lines 19-30) as in claims 8, and 32. The reference also teaches administering the compound orally,(see col. 21, lines

56), as in claim 15, 39 in a tablet or capsule, as in claims 7 and 16. The dosage preferred in the reference is 0.001-50 mg, thus obvious variation of claims 8, 12-13, 16, 32, 36-37,49, 50-53 (see col. 21, lines 30+).

With regards to claims 40-41, 49-53, the reference teaches courses of treatment repeated at appropriate intervals, thus making the claims obvious that the actual dosages of the agents and interval administered will vary according to the particular complex being used, the particular composition formulated, the mode of administration and the particular site, host and disease being treated (see col. 21, lines 22+).

Although kania et al. did not expressly teach the specific dosage ranges it is within the purview of the skilled artisan to optimize the therapeutic range. Based on that the determination of a dosage having the optimum therapeutic index is well within the level of the ordinary skill in the art, and the artisan would be motivated to determine the optimum amounts to get the maximum effect of the drug, hence the reference makes obvious the instant invention.

Although the Kania et al. reference did not teach addition or combination of docetaxel to the compound of formula 1 in claims 17 and 32, one of ordinary skill would have used the teachings suggested by Goodman and Gilman and combined the above compound of formula 1 with docetaxel.

Sweeney et al. teach the combination of a vascular endothelial cell growth factor with docetaxel (VEGF).

Goodman and Gilman teach that anti cancer drugs can be combined with antineoplastic drugs. Wherein Goodman and Gilman teach adjuvant chemotherapy (see page 1225 and 1230) therefore one of ordinary skill in the art would have been motivated to add an antineoplastic drug to the compound formula I for treatment of cancer. Despite such disclosure or teaching, the Kania reference teaches that he inventive compounds may be used advantageously in combination with other known therapeutic agents. For example, compounds of Formula I, II, III, or IV which possess antiangiogenic activity may be co-administered with cytotoxic chemotherapeutic agents, such as taxotere.

One of ordinary skill in the art would have been motivated to combine the teachings of Kania et al with that of Sweeney et al, because in the Sweeney et al reference a VEGF (Applicant's compound is known as a VEGF) compound was used with docetaxel, therefore motivating one of ordinary skill to switch the compound of Sweeney et al. with that of Kania et al. and combine with docetaxel because it is well know in the art of cancer that adjuvant therapy are used to give synergistic effect to the cell proliferation.

Thus, the claimed invention was prima facia obvious to make and use at the time it was made.

Maintained Double Patenting

Claims 8, 12-13 15-16, 32, 36-37, 39-41 and 49-53 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim **1 - 11** of U.S. Patent **7141581**. Although the conflicting claims are not identical, they are not patentably distinct from each other. The reasons are as follows:

Both applications recite using the same compositions and/or derivatives thereof. See instant application claims 8, 12-13 15-16, 32, 36-37, 39-41 and 49-53 and copending application claims 1 – 11. The compositions recited in the claims are obvious of each other for the treatment of various types of cancers.

Using the patent specification as a dictionary, it teaches the compound claimed can be administered in a dosage range from 0.001- 50 mg/kg. Based on that the determination of a dosage having the optimum therapeutic index is well within the level of the ordinary skill in the art, and the artisan would be motivated to determine the optimum amounts to get the maximum effect of the drug, hence the reference makes obvious the instant invention.

In view of the foregoing, the copending application claims and the current application claims are obvious variations.

Applicant argues that the patented claims are to a method of treatment with various compounds and without any specific dosing range.

This is found unpersuasive. The claims recite a range, and one of ordinary skill in the art would have been motivated to optimize the dosage and administer an optimal dosage to the patient in need thereof. The specification of the patent, when used as a dictionary, (see col. 25, lines 24-30) teaches an amount of a given agent that corresponds the dosage range claimed in the instant application. The amount will vary depending upon factors such as the particular compound, disease condition and its

severity, the patient's age and weight of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the in the art.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

SVG
5/29/08